REMARKS

Claims 1-16 are pending in the present Application. Claims 3 – 5, 7 – 14 and 16 have been withdrawn and no claims have been cancelled, leaving Claims 1, 2 6 and 15 for consideration upon entry of the present Amendment. Reconsideration and allowance of the claims are respectfully requested in view of the above amendments and the following remarks.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 1, 2, 6 and 15 stand rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over U.S. Patent No. 6,875,619 to Blackburn in view of US 2002/0054835 to Robotti, et al. ("Robotti"). (Office Action dated 08-06-2008, page 3) Applicants respectfully traverse this rejection.

In making the rejection, the Examiner has stated that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ thermoreversible gels in a system of the primary reference for the known and expected result of providing an alternative means recognized in the art to achieve the same result, control of the flow of fluids with a microfluidic device, and for advantages discussed by the reference of Robotti." (Office Action dated 08-06-2008, page 4)

For an obviousness rejection to be proper, the Examiner must meet the burden of establishing that all elements of the invention are disclosed in the prior art; that the prior art relied upon, or knowledge generally available in the art at the time of the invention, must provide some suggestion or incentive that would have motivated the skilled artisan to modify a reference or combined references; and that the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was make. *In re Fine*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). The obviousness inquiry also requires consideration of common knowledge and common sense. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1742-43 (2007); *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1367 (Fed. Cir. 2006) ("Our suggestion test is in actuality quite flexible and not only permits, but requires, consideration of common knowledge and common sense.")

Claim 1 is directed to a PCR (polymerase chain reaction) device comprising an inlet through which a biochemical fluid is injected; an outlet through which the biochemical fluid is discharged; a PCR channel positioned between the inlet and the outlet; first and second micro-valves, which control opening and closing of the inlet and the outlet; and a sol-gel transformable material, which transforms from a sol state into a gel state at a temperature lower than DNA denaturation temperature, annealing temperature and extension temperature and higher than room temperature; the sol-gel material transformable material being positioned in the first and second micro-valves; the sol-gel material being operative to control the opening and closing of the first and second micro-valves.

Blackburn is directed to a variety of microfluidic devices with configurations that include the use of biochannels or microchannels comprising arrays of capture binding ligands to capture target analytes in samples. (see Abstract) As the Examiner contends, Blackburn discloses a PCR device that includes an inlet; an outlet; a PCR channel (22); a first microvalve (32); and a second microvalve (34). (Office Action dated 08-06-2008, page 4) Blackburn does not teach a valve having a gel that can reversibly change its state to permit the valves to open and close.

Robotti teaches micro-fluid devices and methods for their uses. (see Abstract) Robotti teaches that the device comprises at least one micro-valve comprising a phase reversible material e.g., a reversible gel that reversibly changes its state in response to an applied stimulus, e.g., a thermoreversible gel. (see Abstract) Robotti lists methyl cellulose as a gel material. (see paragraph [0033]) Robotti does not teach that the channel disposed between micro-valves can be used for polymerase chain reactions. Robotti also does not teach a material that transforms from a sol state into a gel state at a temperature lower than DNA denaturation temperature, annealing temperature and extension temperature and higher than room temperature.

One of ordinary skill in the art would not have combined Blackburn with Robotti because they teach away from each other. In particular, the channels sizes disclosed by Robotti are much larger than those disclosed by Blackburn. One of ordinary skill in the art noting these disparate teachings between Robotti and Blackburn would not have combined references in the manner made by the Examiner. If the valves disclosed by Robotti were included in the device of Blackburn it would militate against the teachings of Blackburn. In addition, if the valves of

Robotti were to be included in the device of Blackburn, there would be massive discontinuities in walls of the microfluid channels prescribed by Blackburn. Blackburn does not desire this.

In the manufacturing of the device Blackburn teaches that:

> The lamination process involves the application of pressure to the stacked layers. For example, in the conventional lamination process, a uniaxial pressure of about 1000 to 1500 psi is applied to the stacked green-sheet layers that is then followed by an application of an isostatic pressure of about 3000 to 5000 psi for about 10 to 15 minutes at an elevated temperature, such as 70° C. Adhesives do not need to be applied to bind the green-sheet layers together when the conventional lamination process is used.
>
> However, pressures less than 2500 psi are preferable in order to achieve good control over the dimensions of such structures as internal or external cavities and channels. Even lower pressures are more desirable to allow the formation of larger structures, such as cavities and channels. For example, if a lamination pressure of 2500 psi is used, the size of well-formed internal cavities and channels is typically limited to no larger than roughly 20 microns. Accordingly, pressures less than 1000 psi are more preferred, as such pressures generally enable structures having sizes greater than about 100 microns to be formed with some measure of dimensional control. Pressures of less than 300 psi are even more preferred, as such pressures typically allow structures with sizes greater than 250 microns to be formed with some degree of dimensional control. Pressures less than 100 psi, which are referred to herein as "near-zero pressures," are most preferred, because at such pressures few limits exist on the size of internal and external cavities and channels that can be formed in the multilayered structure.

(Col. 19, lines 38 – 65) While Blackburn teaches that various pressures may be used to manufacture a device with different channel sizes, it desires dimensional control of the surfaces of the microchannel. Blackburn further states that:

> The microfluidic channels of the present invention are channels generally less than 200 microns in plastic with molding or embossing technology. The channels need to be of the dimension to support pumping of the microfluidic system The microfluidic channel may have any shape, for example, it may be linear, serpentine, arc shaped and the like. The cross-sectional dimension of the channel may be

> square, rectangular, semicircular, circular, etc. There may be multiple and interconnected microchannels with valves to provide for recirculation.

(Col. 23, lines 49 – 59)

Blackburn also teaches that:

> In general, the microfluidic devices of the invention are generally referred to as "mesoscale" devices. The devices herein are typically designed on a scale suitable to analyze microvolumes, although in some embodiments large samples (e.g. cc's of sample) may be reduced in the device to a small volume for subsequent analysis. That is, "mesoscale" as used herein refers to chambers and microchannels that have cross-sectional dimensions on the order of 0.1 μm to 500 μm. The mesoscale flow channels and wells have preferred depths on the order of 0. 1 μm to 100 μm, typically 2-50 μm. The channels have preferred widths on the order of 2.0 to 500 μm, more preferably 3-100 μm.

(Col. 25, line 63 – Col. 26, line 7) While Blackburn teaches that pressure can be varied to produce different sized channels, it also teaches that the maximum dimension for a microfluidic channel is 500 micrometers (see Col. 26, line 4) and that the maximum cross-sectional area is 100 micrometers X 500 micrometers = 50,000 square micrometers. (see Col. 26, lines 4 – 7) The maximum cross-sectional area of a channel as prescribed by Blackburn is therefore equal to 50,000 square micrometers, which is equal to 0.0005 square centimeters.

Robotti, on the other hand, teaches that:

> Generally, the micro-fluidic devices in which the subject valves find use will have at least one micro-compartment positioned at some point in the fluid flow path, where the term "micro-compartment" means any type of structure in which micro-volumes of fluid may be contained, and includes micro-chambers, micro-channels, micro-conduits and the like. Depending on the nature of the micro-compartment, the micro-compartment may be the entire fluid flow path through the device, e.g. where the fluid flow path is a micro-channel, as described infra, or occupy only a portion of the fluid flow path of the device. The term micro-chamber, as used herein, means any structure or compartment having a volume ranging from about 1 μl to 500 μl, having cross-sectional areas ranging from about **0. 05 cm^2** with a chamber depth of 200 μm to 5 cm^2 with a chamber depth

> of 1 mm; usually from about 10 μl to 500 μl, having a cross-sectional area ranging from about 0.5 cm^2 with a chamber depth of 200 μm to about 5 cm^2 with a chamber depth of 1 mm; and more usually from about 20 μl to 200 μl having a cross-sectional area ranging from about 1 cm^2 with a chamber depth of 200 μm to about 4 cm^2 with a chamber depth of 500 μm.

(see paragraph [0024]) Thus the minimal cross-sectional area for the micro-chamber or micro-channel prescribed by Robotti is 0.05 square centimeters, which is at least 100 times larger than the cross-sectional area prescribed by Blackburn. This larger area prescribed by Blackburn is due to the gelatinous characteristics of the gels that activate the valves.

One of ordinary skill in the art reading these dissonant teachings of Blackburn and Robotti would not have combined references in the manner made by the Examiner. In addition, the Applicants would like to submit that because of the large difference in sizes of the microchannels prescribed by Blackburn and Robotti, one of ordinary skill in the art would not be able to use a valve prescribed by Robotti in the device of Blackburn. The use of the valve prescribed by Robotti in the device disclosed by Blackburn would lead to major discontinuities in fluid flow in the microchannels. One of ordinary skill in the art examining Blackburn and noting his statement (underlined above) that there must be dimensional control over the microchannels would also not want to add a significant discontinuity to accommodate the valves of Robotti, especially since Blackburn's devices require smaller dimensions for its microchannels. In addition, it is not clear whether the gel disclosed by Robotti would even be able to flow in the fine channels disclosed by Blackburn.

Applicants further maintain that the Examiner has used an improper standard in arriving at the rejection of the above claims under section 103, based on improper hindsight, which fails to consider the totality of applicant's invention and to the totality of the cited references. More specifically the Examiner has used Applicant's disclosure to select portions of the cited references to allegedly arrive at Applicant's invention. In doing so, the Examiner has failed to consider the teachings of the references as a whole in contravention of section 103, including the disclosures of the references, which teach away from Applicant's invention.

Section 103 sets out the test for obviousness determinations. It states, in pertinent part, that such determinations are to be made by consideration of

> . . . the differences between subject matter sought to be patented and the prior art such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the [pertinent] art.

In making a Section 103 rejection, the Examiner bears the burden of establishing a prima facie case of obviousness. *In re Fine*, 5 U.S.P.Q. 2d 1596, 1598 (Fed. Cir. 1998). The Examiner ". . . can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in art would lead that individual to combine the relevant teachings of the references". *Id.*

In addition to noting that Blackburn is not combinable with Robotti, the Applicants would like to take this opportunity to point out to the Examiner the advantages of the claimed device.

Using the present invention, the inlet and an outlet of a PCR device can be simply opened or closed using a sol-gel micro-valve according to the present invention, without requiring an additional heat source. Due to the structural simplicity of the micro-valve, PCR devices can be easily mounted on a micro-chip, such as a lab-on-a-chip, when using the micro-valve according to the present invention, based on micro-processing technology applied to silicon, glass, polymers. The PCR device can be miniaturized to be portable. In addition, the micro-valve according to the present invention prevents biological fluid in the PCR device from evaporating or flowing out of the device, thereby enabling DNA amplification using a constant amount of biochemical fluid. Compared with conventional complicated micro-metering systems frequently used even when handing a trace of biochemical fluid on the order of microliters and picoliters, the micro-valve according to the present invention can be simply operated by just injecting a sol-gel transformable material into inlet and outlet regions of a PCR channel. Furthermore, the injection of the sol-gel transformable material allows an accurate amount of biochemical fluid to be injected into the PCR device, as well as preventing evaporation of the biological fluid to be amplified. The injection of an accurate amount of a biochemical sample prevents waste of the biochemical fluid. In addition, the micro-valve according to the present invention initiates its operation spontaneously at the start of amplification and terminates its function as a valve when the amplification finishes, thereby enabling a rapid transfer of the biochemical fluid for a subsequent process.

In summary, while Blackburn and Robotti teach all of the claimed elements, they are not combinable without a major discontinuity in the walls of the microchannels. These references teach away from one another and one of ordinary skill noting the disparity in the dimensions prescribed by the two references would not have sought to combine them in the manner made by the Examiner.

For this reason at least, the Applicants believe that the Examiner has not made a prima facie case of obviousness over Blackburn in view of Robotti. The Applicants respectfully request a withdrawal of the obviousness rejection and an allowance of the claims.

Conclusion

It is believed that the foregoing amendments and remarks fully comply with the Office Action and that the claims herein should now be allowable to Applicants. Accordingly, reconsideration and allowance are requested.

If there are any additional charges with respect to this Amendment or otherwise, please charge them to Deposit Account No. 06-1130.

Respectfully submitted,

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